Journal of the Pediatric Infectious Diseases Society

ORIGINAL ARTICLE

Multidrug- and Carbapenem-Resistant *Pseudomonas aeruginosa* in Children, United States, 1999–2012

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Background. *Pseudomonas aeruginosa* is a common cause of healthcare-associated infection. Multidrug-resistant (MDR) (>3 classes) and carbapenem-resistant (CR) *P aeruginosa* are significant threats globally. We used a large reference-laboratory database to study the epidemiology of *P aeruginosa* in children in the United States.

Methods. Antimicrobial susceptibility data from the Surveillance Network were used to phenotypically identify MDR and CR *P aeruginosa* isolates in children aged 1 to 17 years between January 1999 and July 2012. Logistic regression analysis was used to calculate trends in the prevalence of MDR and CR *P aeruginosa*. Isolates from infants (<1 year old) and patients with cystic fibrosis were excluded.

Results. Among the isolates tested, the crude proportion of MDR *P aeruginosa* increased from 15.4% in 1999 to 26% in 2012, and the proportion of CR *P aeruginosa* increased from 9.4% in 1999 to 20% in 2012. The proportion of both MDR and CR *P aeruginosa* increased each year by 4% (odds ratio [OR], 1.04 [95% confidence interval (CI), 1.03–1.04] and 1.04 [95% CI, 1.04–1.05], respectively). In multivariable analysis, both MDR and CR *P aeruginosa* were more common in the intensive care setting, among children aged 13 to 17 years, in respiratory specimens, and in the West North Central region. In addition, resistance to other antibiotic classes (aminoglycosides, fluoroquinolones, cephalosporins, and piperacillin-tazobactam) often used to treat *P aeruginosa* increased.

Conclusions. Rates of MDR and CR *P aeruginosa* infection in children are rising nationally. Aggressive prevention strategies, including instituting antimicrobial stewardship programs in pediatric settings, are essential for combating antimicrobial resistance.

Keywords. carbapenems; child; drug resistance; epidemiology; *Pseudomonas aeruginosa*.

Pseudomonas aeruginosa is a Gram-negative bacterium that causes infections that can lead to significant morbidity and death. It is a complex and formidable adversary that has great genetic "plasticity," which facilitates development of antibiotic-resistance mutations, and striking survival rates in the most diverse environments because of its minimal nutritional requirements and ability to use a variety of carbon sources for energy [1]. The severity of such infections is attributable to the broad range of virulence factors carried by the bacterium, including the type III secretion system, which helps establish infection by injecting effector proteins into host cells and thereby enhancing disease severity [2, 3].

Potentially even more multifaceted are the mechanisms of antibiotic resistance attributed to *P aeruginosa*. Foremost have been enzymes that are able to inactivate β-lactam antibiotics; these intrinsic and acquired β-lactamases include cephalosporinases (which produce extended-spectrum cephalosporin resistance) and carbapenemases (which produce carbapenem resistance). Additional resistance mechanisms rely on enzymatic and target-site modifications (aminoglycoside and fluoroquinolone resistance), alterations in outer membrane permeability, and multidrug efflux pumps. The latter 2 mechanisms often render organisms multidrug resistant (MDR) and leave few treatment options against them [4]. The US Centers for Disease Control and Prevention estimates that each year, 51 000 healthcare-associated *P aeruginosa* infections occur in adults and children, of which 13% (>6000) are MDR and account for 400 deaths [5].

Infections with *P aeruginosa* in children are reported most often in association with pulmonary disease in patients with cystic fibrosis (CF) [6]. In addition, healthy children can experience a variety of *P aeruginosa* infection types, particularly infection of the urinary tract, ear, sinuses, wounds, skin, and connective tissues (cartilage and bone) [7–12]. However, as in adults, serious and systemic, often opportunistic, infections are substantial in children with critical illness, in those who

Received 11 March 2016; editorial decision 24 September 2016; accepted 27 September 2016; published online November 16, 2016.

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Journal of the Pediatric Infectious Diseases Society 2017;6(4):352–9

DOI: 10.1093/jpids/piw064

require ventilator support, and in patients who are immunocompromised and/or have a hematologic-oncologic disease [7, 8, 13–18].

The majority of *P aeruginosa* studies have examined the effect of these infections on patients with CF. Despite the annual numbers of infection and rising rates of antibiotic resistance, no pediatric studies have assessed national or regional trends in MDR or carbapenem-resistant (CR) *P aeruginosa*. In this study, we investigated the epidemiology of *P aeruginosa* isolates from children, excluding those with CF, and explored trends in antibiotic resistance over a period of 13.5 years.

METHODS

Antibiotic-susceptibility data were obtained from the Surveillance Network (TSN) Database–USA (Eurofin-Medinet, Herndon, VA). The database has been used extensively to characterize national antibiotic-susceptibility trends [19–22]. The network included clinical microbiology laboratories that served approximately 300 hospitals that were selected by the 9 US Census Bureau regional divisions to be geographically representative and representative of hospital size and patient population. Laboratories included in the TSN database were required to submit results from all routine antimicrobial-susceptibility testing performed on site. Categorical result interpretations were based on Clinical Laboratory Standards Institute (CLSI) criteria adopted by the reporting facilities at the time of testing and reflect susceptibilities as reported to clinicians [23]. Individual laboratory data were validated electronically and merged into a central TSN database.

The database includes records with the following information: the identified organism; the tested drug and susceptibility result (susceptible, intermediate-resistant, or resistant); the source of the isolate (blood, urine, wound, respiratory tract, or skin); patient characteristics (age and sex); the healthcare setting in which the patient sample was collected (outpatient [ambulatory], inpatient intensive care unit [ICU], inpatient [non-ICU], or long-term care setting); the geographical location of the facility in which the specimen was collected; and the date of the drug-susceptibility test.

Our analysis considered *P aeruginosa* isolates obtained from all pediatric patients (aged 1–17) who were in an outpatient (ambulatory), inpatient ICU, inpatient non-ICU, or long-term care setting between January 1, 1999, and June 30, 2012. To improve applicability to the general pediatric population, isolates from patients with CF were excluded from the analysis. We also excluded isolates obtained from patients <1 year old, because the epidemiology of MDR and CR *P aeruginosa* in neonates (in particular, infants cared for in the neonatal ICU) likely differs from that in older children and should be analyzed separately. MDR *P aeruginosa* was defined using US Centers for Disease Control and Prevention criteria [24], which included nonsusceptibility to agent(s) in at least 3 of the following 5 antimicrobial classes: cephalosporins (cefepime, ceftazidime), β-lactam/β-lactamase-inhibitor combination (piperacillin, piperacillin-tazobactam), carbapenems (imipenem, meropenem, doripenem), fluoroquinolones (ciprofloxacin, levofloxacin), and aminoglycosides (gentamicin, tobramycin, amikacin). An isolate was deemed CR *P aeruginosa* if it was nonsusceptible to at least 1 of the 3 agents in the carbapenem class (imipenem, meropenem, or doripenem). Only isolates that were tested for all 5 antibiotic classes, including carbapenems, were included in the final analysis.

When duplicate records (with the same patient identification number, drug-susceptibility test, and specimen source) were identified, only the first isolate was included in the analysis. The frequency of MDR and CR *P aeruginosa* is reported as the number of isolates that tested positive divided by the total number of tested isolates included in the analysis. Individual susceptibility results were stratified according to location (ICU, inpatient non-ICU, outpatient, and long-term care facilities), age (1–5, 6–12, and 13–17 years), sex, isolate source (blood, urine, wound, respiratory tract, and skin), annual intervals, and geographic region based on the location of the healthcare facility (East North Central, East South Central, Mid-Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, and West South Central). Because the antibiotic-susceptibility patterns differed among hospitalized and nonhospitalized patients, we examined the distributions of MDR and CR *P aeruginosa* isolates among those obtained from patients in inpatient (ICU or inpatient non-ICU) and outpatient (ambulatory) facilities. In addition, we examined the susceptibility of *P aeruginosa* isolates to all agents in each of the 5 antibiotic classes among the inpatients and outpatients.

Unadjusted trends in the prevalences of MDR and CR *P aeruginosa* were calculated using logistic regression. Multivariable logistic regression analysis was used to estimate the prevalences of MDR and CR *P aeruginosa*, which was adjusted for time (year) and patient characteristics, including age, sex, isolate source, patient location, and geographic region. Confidence intervals (CIs) were calculated using a Wilson score method. A *P* value of <.05 was considered statistically significant. Data were analyzed using the R programming language.

RESULTS

Overall, 87 613 pediatric *P aeruginosa* isolates were identified in the database between 1999 and 2012, of which 77 349 isolates were tested against 5 antibiotic classes, including carbapenems. Of these 77 349 *P aeruginosa* isolates, 15 653 (20.2%)

isolates were MDR, 8763 (11.3%) were CR, and 6510 (8.4%) were both MDR and CR. Overall, the isolates were most often from outpatients (44 158 isolates [57.0%]), a respiratory tract source (47 564 isolates [61.4%]), and 1- to 5-year-old patients (28 879 isolates [37.3%]) (Table 1). The distributions of isolates among male and female patients were similar (38 526 [49.8%] vs 37 555 [48.5%], respectively, excluding isolates from patients with unreported sex). Of the 9 regions in the data set, the largest number of isolates came from the South Atlantic region (13 559 [17.5%]) (Table 1).

Table 1. Distribution of MDR and CR *Pseudomonas aeruginosa* Isolates in Children Aged 1 to 17 Years, 1999–2012*

Characteristic	Total No. of Isolates (N = 77 349)	No. (%) of MDR† Isolates (N = 15 653)	No. (%) of CR‡ Isolates (N = 8763)
Patient setting			
Inpatient	24 234	5123 (32.7)	3317 (37.9)
Inpatient, ICU	7893	2075 (13.3)	1458 (16.6)
Long-term care	332	107 (0.7)	49 (0.6)
Outpatient	44 158	8267 (52.8)	3868 (44.1)
Unknown	732	81 (0.5)	71 (0.8)
Patient sex			
Female	37 555	7639 (48.8)	4192 (47.8)
Male	38 526	7819 (50.0)	4393 (50.1)
Unknown	1268	195 (1.2)	178 (2.0)
Specimen source			
Blood	2093	323 (2.1)	263 (3.0)
Respiratory tract	47 564	12 117 (77.4)	6234 (71.1)
Urine	15 364	1989 (12.7)	1288 (14.7)
Wound	11 870	1196 (7.6)	951 (10.9)
Skin	458	28 (0.2)	27 (0.3)
Age group			
1–5 y	28 879	3657 (23.4)	2541 (29.0)
6–12 y	25 158	4848 (31.0)	2517 (28.7)
13–17 y	23 312	7148 (45.7)	3705 (42.3)
Region§			
East North Central	13 231	2514 (16.1)	1478 (16.9)
East South Central	1886	233 (1.5)	121 (1.4)
Mid-Atlantic	7721	1473 (9.4)	923 (10.5)
Mountain	5299	1026 (6.6)	502 (5.7)
New England	2295	445 (2.8)	273 (3.1)
Pacific	9014	1264 (8.1)	763 (8.7)
South Atlantic	13 559	2488 (15.9)	1370 (15.6)
West North Central	12 465	3888 (24.8)	2067 (23.6)
West South Central	11 879	2322 (14.8)	1266 (14.4)

Abbreviations: CR, carbapenem resistant; ICU, intensive care unit; MDR, multidrug resistant.
*Data source was the Surveillance Network Database–USA.
†Nonsusceptible to at least 1 agent in at least 3 of the following 5 antimicrobial classes: cephalosporins (cefepime, ceftazidime), β-lactam/β-lactamase-inhibitor combination (piperacillin, piperacillin-tazobactam), carbapenems (imipenem, meropenem, doripenem), fluoroquinolones (ciprofloxacin, levofloxacin), and aminoglycosides (gentamicin, tobramycin, amikacin).
‡Nonsusceptible to at least 1 of the 3 agents in the carbapenem class (imipenem, meropenem, doripenem).
§The East North Central region includes Illinois, Indiana, Michigan, Ohio, and Wisconsin; the East South Central region includes Alabama, Kentucky, Mississippi, and Tennessee; the Mid-Atlantic region includes New Jersey, New York, and Pennsylvania; the Mountain region includes Arizona, Colorado, Idaho, Montana, New Mexico, Nevada, Utah, and Wyoming; the New England region includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; the Pacific region includes Alaska, California, Hawaii, Oregon, and Washington; the South Atlantic region includes Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia; the West North Central region includes Iowa, Kansas, Minnesota, Missouri, North Dakota, Nebraska, and South Dakota; and the West South Central region includes Arkansas, Louisiana, Oklahoma, and Texas.

Among MDR and CR isolates, the largest numbers were from respiratory sources (12 117 [77.4%] and 6234 [71.1%], respectively), children aged 13 to 17 years (7148 [45.7%] and 3705 [42.3%], respectively), male patients (7819 [50.0%] and 4393 [50.1%], respectively), an outpatient setting (8267 [52.8%] and 3868 [44.1%], respectively), and the West North Central region (3888 [24.8%] and 2067 [23.6%], respectively) (Table 1).

Overall, among the various patient and isolate characteristics, the proportion of MDR and CR *P aeruginosa* isolates was higher in inpatients than in outpatients (Table 2). Among them, the highest proportions of MDR and CR isolates were from lower respiratory sources (28.0% and 17.5% [inpatients] and 23.8% and 10.1% [outpatients], respectively), children aged 13 to 17 years (32.4% and 20.3% [inpatients] and 29.5% and 12.9% [outpatients]), and the West North Central region (33.9% and 24.3% [inpatients] and 29.6% and 12.1% [outpatients]) (Table 2).

An analysis of linear trends using logistic regression revealed a significant increase in the proportion of both MDR (15.4%–26.0%; $P < .001$) and CR (9.4%–20.0%; $P < .001$) *P aeruginosa* isolates between 1999 and 2012 (Figure 1). With each year, the proportions of MDR and CR *P aeruginosa* isolates increased by 4% (odds ratios [ORs], 1.04 [95% CI, 1.03–1.04] and 1.04 [95% CI, 1.04–1.05], respectively). The proportions of both MDR and CR *P aeruginosa* isolates increased significantly in all age categories and patient locations except among children aged 13 to 17 years in an inpatient setting (Supplementary Table 1). After the data were adjusted for year, patient, and isolate characteristics, patients who were 13 to 17 years old had the highest prevalences of MDR and CR *P aeruginosa*, which were 3 times (adjusted ORs [aORs], 3.0 [95% CI, 2.8–3.1]) and 2 times (aOR, 1.96 [95% CI, 1.8–2.0]) higher than those in 1- to 5-year-old children (Table 3). Among patient locations, long-term care residents had the highest prevalence of MDR *P aeruginosa*, 2.3 times (aOR, 2.3 [95% CI, 1.8–2.9]) higher than that in the outpatient locations, whereas the CR *P aeruginosa* prevalence was highest in ICUs, 2.6 times (95% CI, 2.4–2.8] higher than that in outpatient locations (Table 3). Among specimen sources, respiratory specimens had the highest prevalences of MDR and CR *P aeruginosa*, 1.8 times (aOR, 1.8 [95% CI, 1.6–2.1]) and 1.2 times (aOR, 1.2 [95% CI, 1.0–1.3]) higher than that of specimens obtained from blood. Among the geographic regions, MDR and CR *P aeruginosa* isolates were most prevalent in the West North Central Region, 1.8 times (aOR, 1.8 [95% CI, 1.7–1.9]) and 1.5 times (aOR, 1.5 [95% CI, 1.3–1.6]) higher than that in the East North Central region of United States.

P aeruginosa resistance to other frequently used antibiotic classes was higher among inpatient isolates than among outpatient isolates with the exception of aminoglycosides (amikacin, gentamicin, and tobramycin) (Table 4 and Supplementary

Table 2. Proportion of MDR and CR *Pseudomonas aeruginosa* Isolates in Inpatient and Outpatient Children Aged 1 to 17 Years, 1999–2012*

Characteristic	Inpatient†			Outpatient		
	Total No. of Isolates (N = 32 127)	No. (%) of MDR‡ Isolates (N = 7198)	No. (%) of CR§ Isolates (N = 4775)	Total No. of Isolates (N = 44 158)	No. (%) of MDR‡ Isolates (N = 8267)	No. (%) of CR§ Isolates (N = 3868)
Patient sex						
Female	14 811	3329 (22.5)	2149 (14.5)	22 271	4238 (19.0)	1990 (8.9)
Male	16 826	3763 (22.4)	2529 (15.0)	21 120	3941 (18.7)	1798 (8.5)
Unknown	490	106 (21.6)	97 (19.8)	767	88 (11.5)	80 (10.4)
Specimen source						
Blood	1575	269 (17.1)	225 (14.3)	495	52 (10.5)	37 (7.5)
Respiratory tract	18 755	5247 (28.0)	3287 (17.5)	28 214	6729 (23.8)	2863 (10.1)
Urine	5325	824 (15.5)	594 (11.2)	9760	1129 (11.6)	670 (6.9)
Wound	6319	845 (13.4)	659 (10.4)	5391	343 (6.4)	283 (5.2)
Skin	153	13 (8.5)	10 (6.5)	298	14 (4.7)	15 (5.0)
Age group						
1–5 y	13 869	2298 (16.6)	1658 (12.0)	14 573	1293 (8.9)	839 (5.8)
6–12 y	8988	1893 (21.1)	1239 (13.8)	15 832	2914 (18.4)	1257 (7.9)
13–17 y	9270	3007 (32.4)	1878 (20.3)	13 753	4060 (29.5)	1772 (12.9)
Region						
East North Central	5030	1162 (23.1)	803 (16.0)	8048	1388 (16.6)	661 (8.2)
East South Central	1166	157 (13.5)	85 (7.3)	678	75 (11.1)	34 (5.0)
Mid-Atlantic	2950	738 (25.0)	498 (16.9)	4605	696 (15.1)	401 (8.7)
Mountain	2058	415 (20.2)	207 (10.1)	3238	610 (18.8)	295 (9.1)
New England	561	107 (19.1)	85 (15.2)	1727	338 (19.6)	188 (10.9)
Pacific	4283	741 (17.3)	479 (11.2)	4352	484 (11.1)	254 (5.1)
South Atlantic	5298	1006 (19.0)	704 (13.3)	8122	1459 (18.0)	650 (8.0)
West North Central	4564	1549 (33.9)	1110 (24.3)	7898	2339 (29.6)	957 (12.1)
West South Central	6217	1323 (21.3)	804 (12.9)	5490	928 (16.9)	428 (7.8)

Abbreviations: CR, carbapenem resistant; MDR, multidrug resistant.

*Data source was the Surveillance Network Database–USA.

†Includes inpatient and inpatient intensive care unit locations.

‡Nonsusceptible to at least 1 agent in at least 3 of the following 5 antimicrobial classes: cephalosporins (cefepime, ceftazidime), β-lactam/β-lactamase-inhibitor combination (piperacillin, piperacillin-tazobactam), carbapenems (imipenem, meropenem, doripenem), fluoroquinolones (ciprofloxacin, levofloxacin), and aminoglycosides (gentamicin, tobramycin, amikacin).

§Nonsusceptible to at least 1 of the 3 agents in the carbapenem class (imipenem, meropenem, doripenem).

Table 2). Resistance to gentamicin was high among both inpatients and outpatients over the study period. Although doripenem resistance among inpatients was highest, only 87 isolates were tested between 2008 and 2012 (Table 4). In addition, gentamicin resistance increased over the study period among both the inpatient (23.8% in 1999–2003 to 26.1% in 2008–2012) and outpatient (25.7% in 1999–2003 to 28.4% in 2008–2012) isolates. Among the antibiotics, piperacillin-tazobactam had the least resistance in the inpatient and outpatient isolates. However, resistance to piperacillin-tazobactam increased over the study period among both the inpatient (7.9% in 1999–2003 to 12.5% in 2008–2012) and outpatient (3.2% in 1999–2003 vs 4.4% in 2008–2012) isolates (Table 4).

DISCUSSION

We observed significant increases in the prevalences of MDR and CR *P aeruginosa* isolates from US children between 1999 and 2012. Children admitted to an ICU, with a respiratory tract infection, between the ages of 13 and 17 years, and in the West North Central region of the United States had higher prevalences of MDR and CR *P aeruginosa*. Although the prevalence of MDR *P aeruginosa* in long-term care settings was highest, overall, there were not enough isolates from this setting in our data set to derive a robust conclusion.

Antibiotic resistance in *P aeruginosa*, arguably the most resistance-prone healthcare pathogen, is not a new phenomenon; however, antibiotic-resistant infections continue to become more complex and difficult to treat and are associated with significant hospital and societal costs [25]. *P aeruginosa* has a unique ability to survive in harsh environments; mechanisms that protect this bacterium from the actions of antibiotics include intrinsic resistance associated with chromosomally encoded β-lactamase enzymes; quorum-sensing proteins that let the bacteria communicate, which facilitates the formation of protective biofilms; efflux pumps that remove threats from the bacterial cytoplasm; structural topoisomerase mutations that deactivate fluoroquinolones; and cell wall porin alterations and outer membrane changes that prevent entry of antibiotics or other threats to bacterial survival and that work in concert to prevent antibiotics from eradicating it [4, 26]. The acquisition of mobile genetic elements, such as plasmids and transposons

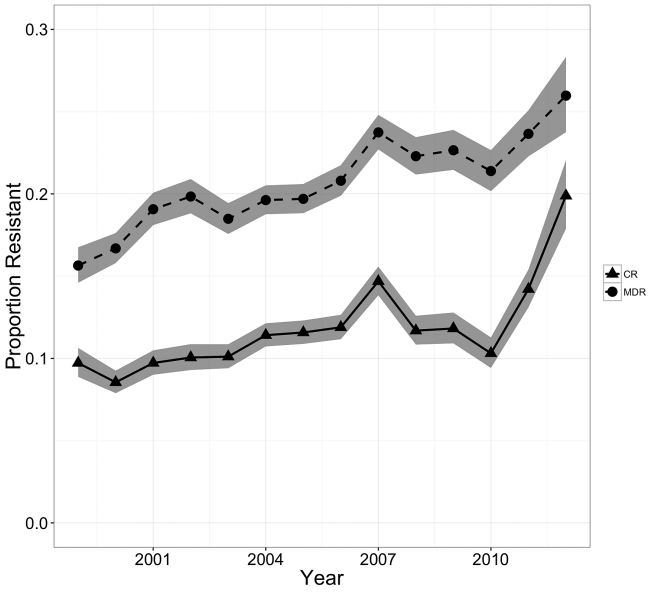

Figure 1. National trends in prevalence of carbapenem-resistant (CR) and multidrug-resistant (MDR) *Pseudomonas aeruginosa* isolates from children >1 year old (data are from the Surveillance Network Database–USA database, 1999–2012). The proportion of MDR and CR *P aeruginosa* isolates increased significantly by 4% every year (odds ratios, 1.04 [95% confidence interval (CI), 1.03–1.04] [*P* for trend < .001] and 1.04 [95% CI, 1.04–1.05] [*P* for trend < .001], respectively).

that harbor genes encoding for carbapenemases, aminoglycoside-modifying enzymes, and fluoroquinolone resistance determinants, contribute to high levels of resistance to last-line antibiotics such as the carbapenems, (imipenem, meropenem, and doripenem) and to the expression of MDR phenotypes among isolates [4, 27, 28].

Because ICUs harbor critically ill and immunocompromised children and involve high antibiotic and device usage rates, it is not surprising that we found high prevalences of MDR and CR *P aeruginosa* isolates in ICU patients [29]. High prevalences of MDR and CR *P aeruginosa* isolates among older children might relate to an increasing number of children with a medically complex condition who have frequent exposure to the healthcare environment [30].

With increasing drug resistance, the antibiotics used for effective treatment have expanded, and the selection pressure for the MDR and CR phenotypes continues to grow; institutional pan-drug-resistant *P aeruginosa* outbreaks in the United States have been described [31]. Colonization of *P aeruginosa* is associated with a polyclonal endemicity in hospitalized patients [32], and for decades, traditional infection-control practices have failed to control it [33]. The ubiquitous presence of *P aeruginosa* in the environment, water sources, and healthcare settings has prevented control of its acquisition among our most vulnerable patients, including critically ill patients,

Table 3. Logistic Model of Multidrug- and Carbapenem-Resistant *Pseudomonas aeruginosa* Adjusted for Patient and Isolate Characteristics in Children Aged 1–17 Years, 1999–2012

	MDR *P aeruginosa* (N = 77 439)		CR *P aeruginosa* (N = 77 439)	
Isolate Characteristic*	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Linear trend, 1999–2012	1.031 (1.025–1.036)	<.001	1.037(1.030–1.044)	<.001
Age (reference, 1–5 y)				
6–12 y	1.709 (1.628–1.794)	<.001	1.243 (1.171–1.319)	<.001
13–17 y	3.084 (2.945–3.230)	<.001	2.034 (1.925–2.150)	<.001
Patient location (reference, outpatient)				
Inpatient	1.442 (1.382–1.503)	<.001	1.908 (1.813–2.009)	<.001
Inpatient, ICU	1.790 (1.687–1.899)	<.001	2.589 (2.418–2.772)	<.001
Long-term care	2.322 (1.817–2.949)	<.001	1.881 (1.364–2.539)	<.001
Unknown	0.932 (0.728–1.178)	.567	1.765 (1.360–2.255)	<.001
Specimen source (reference, blood)				
Respiratory tract	1.818 (1.608–2.062)	<.001	1.157 (1.013–1.327)	.035
Skin	0.399 (0.261–0.589)	<.001	0.572 (0.370–0.851)	.008
Urine	0.789 (0.693–0.902)	<.001	0.734 (0.636–0.850)	<.001
Wound	0.593 (0.518–0.681)	<.001	0.661 (0.571–0.767)	<.001
Region (reference, East North Central)				
East South Central	0.676 (0.581–0.783)	<.001	0.531 (0.435–0.643)	<.001
Mid-Atlantic	0.973 (0.903–1.048)	.468	1.045 (0.956–1.143)	.332
Mountain	1.107 (1.107–1.204)	.019	0.900 (0.807–1.003)	.059
New England	0.818 (0.727–0.918)	.001	0.985 (0.854–1.133)	.836
Pacific	0.693 (0.641–0.748)	<.001	0.663 (0.603–0.728)	<.001
South Atlantic	0.917 (0.860–0.978)	.009	0.853 (0.787–0.924)	<.001
West North Central	1.830 (1.721–1.947)	<.001	1.454 (1.349–1.568)	<.001
West South Central	1.031 (0.965–1.101)	.370	0.874 (0.805–0.948)	.001

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CR, carbapenem resistant; ICU, intensive care unit; MDR, multidrug resistant.
*Sex was not considered, because no significant differences in the distributions of isolates between male and female patients were found.

Table 4. *Pseudomonas aeruginosa* Antibiotic Susceptibilities in Inpatient and Outpatient Children Aged 1–17 Years, 1999–2012*

	% Resistant Isolates (n)†		
Antibiotic	1999–2003	2004–2007	2008–2012
Inpatients			
Amikacin	13.7 (12 928)	12.9 (10 990)	13.2 (7079)
Cefepime	16.5 (10 747)	18.5 (10 809)	19.7 (7119)
Ceftazidime	15.7 (14 239)	19.1 (12 112)	18.0 (7398)
Ciprofloxacin	13.4 (13 972)	15.4 (12 231)	16.2 (7793)
Doripenem	0 (0)	0 (0)	27.6 (87)
Gentamicin	23.8 (15 367)	24.4 (12 803)	26.1 (7845)
Imipenem	11.7 (13 128)	15.4 (10 612)	15.7 (6185)
Levofloxacin	12.4 (9967)	14.2 (9377)	16.9 (5221)
Meropenem	10.5 (5539)	15.5 (7965)	16.1 (5622)
Piperacillin	12.9 (11 560)	13.9 (7596)	16.4 (3164)
Piperacillin-tazobactam	7.9 (9497)	8.9 (11 180)	12.5 (7393)
Tobramycin	10.9 (14 430)	12.5 (12 389)	14.2 (7640)
Outpatients			
Amikacin	18.4 (15 710)	20.5 (15 696)	21.8 (11 648)
Cefepime	11.1 (13 215)	11.7 (14 692)	11.9 (10 822)
Ceftazidime	7.3 (17 465)	8.9 (16 432)	7.7 (11 816)
Ciprofloxacin	12.8 (17 472)	14.8 (17 132)	13.6 (12 687)
Doripenem	0 (0)	0 (0)	12.5 (104)
Gentamicin	25.7 (19 616)	27.0 (171 719)	28.4 (12 184)
Imipenem	7.3 (15 687)	9.5 (14 032)	10.0 (10 503)
Levofloxacin	13.6 (11 037)	14.2 (11 243)	13.1 (8252)
Meropenem	5.8 (6491)	7.5 (10 743)	7.4 (9342)
Piperacillin	5.9 (14 547)	7.1 (9040)	7.4 (4365)
Piperacillin-tazobactam	3.2 (10 975)	4.2 (15 188)	4.4 (10 876)
Tobramycin	11.2 (18 316)	14.9 (16 996)	17.3 (12 103)

*Data source was the Surveillance Network Database–USA.
†n indicates the number of isolates tested.

burn victims, immunocompromised patients, and children [29, 34, 35]. However, there have been notable infection-control successes in decreasing organism burdens, particularly with regard to catheter-associated infections [36, 37]. *P aeruginosa* is a common cause of catheter-associated urinary tract infection (CAUTI) and is associated with the formation of antibiotic-resistant biofilms and subsequent risk for severe infections such as bacteremia [38]. National efforts to reduce CAUTIs through detection and prevention programs include a multifaceted approach that involves provider education, microbial surveillance, performance measures, and bundled interventions; successful program implementations have been associated with improved patient outcomes [36, 37].

The increase in MDR *P aeruginosa* strains in children during the study period also might relate to trends in antibiotic-prescribing practices in the United States. Between 2000 and 2010, prescriptions of third- and fourth-generation cephalosporins and other broad-spectrum agents, including fluoroquinolones, increased in children in outpatient settings [39, 40]. Similarly, recent antibiotic-prescribing data from inpatient studies revealed similar findings, indicating increased selection pressure for colonization with MDR strains [41]. High prevalences of MDR and CR *P aeruginosa* isolates in the West North Central region might be associated with the reported high antibiotic consumption in this region [42, 43]. The highest rates of other MDR Gram-negative bacilli in children, such as CR Enterobacteriaceae, were reported in this region also [21].

Antimicrobial stewardship programs, which improve prescribing practices and restrict the use of broad-spectrum antimicrobial agents, have been shown to be highly effective in decreasing the incidence of healthcare-acquired infections, including infection with *P aeruginosa* [44] A 22-hospital survey found that restriction of carbapenem use was successful in reducing the incidence rates of CR *P aeruginosa* over a 5-year period in adult and pediatric patients [38]. A meta-analysis of MDR infections suggested substantial links to antibiotic usage, and improved antibiotic-prescribing practices resulted in reductions in antibiotic-resistant pathogens [45]. These best practices for decreasing antibiotic consumption have been substantiated in pediatrics and in critical care units, which is relevant to our findings of the most dramatic uptrends occurring in young children and those cared for in an intensive care setting [46, 47].

The importance of these initiatives is underscored not only in our findings of increasing MDR and CR *P aeruginosa* isolates but also in the notable increases in resistance to other commonly used therapies, including cefepime, piperacillin-tazobactam, fluoroquinolones (ciprofloxacin and levofloxacin), and aminoglycosides (gentamicin, tobramycin, and amikacin). The high rates of fluoroquinolone resistance in *P aeruginosa* related to the widespread use of this agent (associated with the availability of oral and intravenous formulations) have been well described in adult study reports [48]; however, before this study, fluoroquinolone-resistant *P aeruginosa* was described recently as having a low prevalence in US children, except in patients with CF [49, 50]. Similarly, the findings of high levels of gentamicin resistance in inpatient and outpatient settings might be reflective of the multiple modes of delivery, including topical, inhalation, and intravenous formulations, available to children. Colonization with gentamicin-resistant organisms has been associated with all formulations, including topical formulations [51, 52].

Increasing trends in *P aeruginosa* resistance to various antibiotics in ambulatory settings might reflect improvements in outpatient therapeutic approaches for patients who previously required hospitalization (such as in the care of children with neutropenic cancer or in ventilator-dependent children) [53, 54], or alternatively, notable practices of prescribing long-term prophylactic antibiotics and multiple oral treatment courses for children with recurrent urinary tract infections and/or urinary tract abnormalities [55, 56]. The significant number of tracheal aspirates (~12%) obtained from patients in an outpatient setting (Supplementary Table 3) suggests that, in recent decades, more children with a chronic respiratory disease and/

or a tracheostomy are being managed at home with ventilator support rather than in a long-term care facility and that these children are often monitored in ambulatory ventilator or pulmonology clinics.

However, the frequent need for hospitalization, concern about morbidity and death that result from sepsis, and subsequent exposure to broad-spectrum intravenous antibiotics remains a burden for all of these children [15, 57, 58]. Revolutionary advances in rapid molecular diagnostics for viral and bacterial pathogens are assisting in the identification of patients who might more definitively benefit from antimicrobial therapy and those for whom antibiotics are not indicated [59–61].

Our study has important limitations. First, because the data stemmed from laboratory surveillance, we were not able to distinguish between colonization and true infection, and we could not account for detailed clinical characteristics of the individual patients. Second, as is common with large databases, some uncertainty was introduced by coding discrepancies, as for cases in which patients were treated in a location other than that recorded at admission. Third, although all TSN laboratories apply CLSI methods, minimum inhibitory concentrations (MICs) were not available, and susceptibility testing was not centralized, which introduced some margin of uncertainty as a result of local discrepancies. Fourth, there was a reduction in the number of laboratories that reported data in the final years of the study, which might have affected variations in carbapenem and multidrug resistance; however, the increasing trends and high levels of statistical significance found throughout the study period lessen this concern. Fifth, we do not have more recent data (beyond 2012), because the TSN database was disbanded after 2012; however, these are the only national-level trend data available. Sixth, CLSI breakpoints for piperacillin-tazobactam were lowered in January 2012 [62], which might have contributed to the higher MDR rates in 2012; however, a sensitivity analysis in which the year 2012 was excluded still showed a significant increase in MDR *P aeruginosa* trends. Seventh, we included only isolates that were tested against all 5 classes of antibiotics. Although the distribution of excluded isolates according to patient and isolate characteristics was similar to that of the included isolates (Supplementary Table 4), there is a possibility of both underestimation and overestimation of MDR isolates with exclusion of these isolates. Finally, the observed increases in the rates of MDR and CR *P aeruginosa* over time might partly be a result of clinicians becoming more discerning about which patients to test.

CONCLUSIONS

Infection with MDR or CR *P aeruginosa* is a significant threat to all patients, including children. The results of our study highlight the need for bacterial surveillance, strategies for implementing effective infection-prevention, and antimicrobial stewardship programs. The institution of rapid molecular diagnostic platforms should be considered by all healthcare facilities to guide antibiotic treatment decisions in an effort to reduce the burden of the persistent and continually evolving global threat of extensively drug-resistant organisms.

Supplementary Data

Supplementary Data Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank Drs Robert Bonomo, Kenneth Boyer, and Mary Hayden for their thoughtful comments and guidance.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or the Centers for Disease Control and Prevention.

Financial support. This work was supported directly by The National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grant K08AI112506 to L. K. L.), the Global Antibiotic Resistance Partnership, funded by the Bill and Melinda Gates Foundation (S. G., E. Y. K., J. L., and R. L.), and the Health Grand Challenges Program at Princeton University (R. L.).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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